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(54) Title: PLASTIC OBJECT CONTAINING CHLORHEXIDINE AND A PROCESS FOR PRODUCING THE OBJECT

(57) Abstract

Plastic object intended for extended contact with living tissue, for example catheters, mainly consisting of a hydrophobic plastic, whereby it contains at least in connection with the surface chlorhexidine in a bactericidally effective amount; and process for the manufacture of such plastic objects using extrusion of a thermoplastic.

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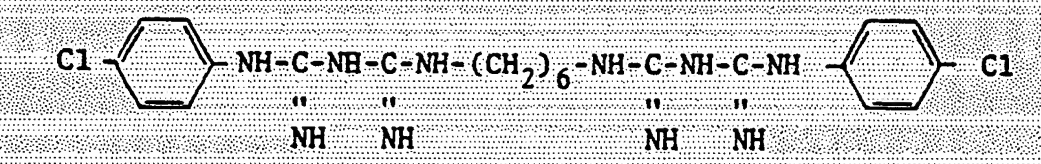
Plastic object containing chlorhexidine and a process for producing the object

The present invention relates to plastic objects which in practical use are in extended contact with living tissue. The invention also relates to a process for the manufacture of such plastic object. Plastic objects are known which are intended for implantation in the body or insertion in different parts of the body. Examples of such plastic objects are catheters, plastic prostheses of different types etc. One problem in using such plastic objects consists in the extended contact with surrounding tissue causing undesirable infections. Such problems arise for example nearly always in connection with urinarytract catheters resulting, in addition to the inconveniencies for the patient that the infection causes, that the catheter has to be replaced at relatively short intervals.

Different attempts to solve the problem have been made, mainly by trying to attach to the surface of the catheters antibiotically or germicidally acting substances. However, hitherto no satisfactory solution to the problem has been found.

The present invention thus has for its object to provide a plastic object of the above-described type whereby the problem indicated is eliminated or at any rate substantially reduced. The invention also has for an object to provide a process for the manufacture of such plastic objects.

The present invention is based on the use of the bactericidally active substance chlorhexidine known per se the systematic chemical name of which is 1,1'-hexamethylenebis[5-(4-chlorophenyl)biguanide] having the following structural formula:



This substance of the trivial name chlorhexidine is an active antiseptic with bactericidal effect against gram-positive as well as gram-negative bacteria. In connection with the present invention it has now been surprisingly found that the substance chlorhexidine can be introduced in hydrofobic plastics so that these, at least in connection with the surface of the plastic object, contain the substance chlorhexidine . Thereby, the plastic

object in use causing extended contact with living tissue obtains a substantially reduced infection risk in that bacterial growth in connection with the plastic object is avoided or at any rate strongly inhibited. It is surprising that the bactericidal properties of the chlorhexidine are maintained in spite of the fixation in the hydrofobic plastic, and even if the invention is not limited to any specific theory concerning the mechanism of fixation it is conceivable that the chlorhexidine molecule is folded double in some manner so that the hydrofobic hydrocarbon chain in the middle is fixed in the plastic, whereas the bactericidally active terminal parts are externally accessible.

The chlorhexidine may be baked into the plastic mainly only in the surface layer of the plastic object but may alternatively be distributed across the whole mass of the plastic object.

In view of the process for the manufacture of the plastic objects according to the invention which will be described in detail below suitable plastics for the manufacture of the plastic objects are hydrofobic plastics of a thermoplastic nature. The character of the plastic or polymer in other respects is not chritical, since the chlorhexidine seems to be fixed by some sort of mechanical anchorage whereby the exact chemical composition of the plastic is not critical. Particularly preferred plastics or polymers are thermoplastic products prepared by a addition polymerisation from vinyl monomers, such as ethylene, vinyl chloride, styrene or propylene. Also other polyolefins are useful, for example polybutenes. Particularly preferred are polyethylene, polypropylene and polyvinyl chloride.

A bactericidally effective amount of the chlorhexidine is suitably at least about 0.1% by weight based on the part of the plastic material containing chlorhexidine. A preferred quantity range with regard to chlorhexidine is about 0.5 to about 1% by weight.

The invention provides, as previously indicated, also the process for the manufacture of the plastic object, and this process comprises extrusion of a thermoplastic in a manner known per se, the thermoplastic in connection with the extrusion

but before cooling or self-cooling of the thermoplastic after leaving the nozzle being supplied with chlorhexidine in solid form in the desired quantity. For the manufacture of plastic objects wherein the chlorhexidine is substantially evenly distributed in the whole mass of the plastic object the chlorhexidine is added to the thermoplastic before feeding into the extruder and is suitably admixed with the plastic granules used before transferring same to the place of feeding the extruder.

Alternatively, the chlorhexidine can be supplied to the thermoplastic in connection with the extrusion nozzle, and in this alternative procedure the chlorhexidine is found mainly only in the surface layer of the plastic object. This latter alternative does, of course, result in a lesser consumption of chlorhexidine, since the other parts of the plastic object will not contain the substance in question.

The manufacturing technique is wholly conventional and can be carried out using a plastic extruder, for example equipped with a feeding funnel, a feeder screw surrounded by a temperature controlling mantle, heating means and a suitable nozzle. In this case the chlorhexidine may thus be supplied either to the plastic material and admixed therein before feeding into the feeding funnel or may be supplied at a later stage in the extrusion process, either before or in connection with the nozzle by spraying the chlorhexidine in pulverulent form.

The present invention will in the following be described in connection with non-limiting examples. The plastics used in these examples are polyethylene and polyvinylchloride of the types shown. The area of use of the plastic object according to the invention is of such nature that the material used should, of course, possess medicinal tolerability.

In the following examples test catheters are manufactured by extrusion in a conventional extruder having a feeding funnel, a feeder screw surrounded by a temperature controlling mantle for a heat-transfer medium and the usual means in connection with the extrusion nozzle. The chlorhexidine is supplied in pulverulent form either by spraying of the plastic material in the area immediately ahead of the extrusion nozzle or by admixture in the plastic material used before feeding into the feeding funnel.

In the former case no exact knowledge will be obtained about the contents of chlorhexidine in the surface of the catheter prepared, whereas in this later case the content can be calculated starting from the quantity of chlorhexidine admixed with the plastic.

EXAMPLE 1

In the present example there is used as a starting material for the manufacture of catheters a PVC-plastic obtained from Thevinyl AB, Sweden, which is stated to be of the type GFM, i.e. PVC of suspension type. This plastic is medicinally tolerable and accepted by FDA, USA. The chlorhexidine is supplied by spraying of powder into the extruder immediately before entering of the material into the extrusion nozzle.

For investigating the bactericidal properties of the catheters made tests were performed using a number of different test bacteria. The test strains were taken from positive urinary cultures showing significant growth. As nutrient media there were used nutrient broth (Bidife, Milano, Italy) prepared according to the instructions of the manufacturer and transferred in quantities of 5 mls in test tubes before sterilization. As a solid medium there was used test agar (PDM antibiotic sensitivity medium, AB Biodisk) prepared according to the instructions and transferred into 9 cms sterile petridishes.

For the manufacture of inoculate there was used (a) coliform bacteria. Suspension of 5 colonies in 1 ml sterile 0.9% saline. While using a graded plastic loop 1 µl of suspension was transferred into 1 ml of saline.

(b) staphylococci, enterococci, streptococci Group B. 5 colonies are suspended in 5 mls 0.9% saline;

(c) beta- and alphastreptocci. 10 colonies are suspended in 1 ml 0.9% saline.

A tube containing 5 mls of broth was inoculated with one drop (0.025 ml) of bacterial suspension. A 4 cm piece of the catheter is placed in tubes and incubation is performed over night at 37°C. The growth is visually controlled. Each series consists of treated catheters and controls with untreated catheters and only inoculated tubes.

The results of the experiments as carried out are shown in following Table 1. In all cases growth of the test strain was observed both in tubes with treated catheters and with untreated catheters.

TABLE 1

Bacterial strain	Number of tests	Number showing growth	No growth
Esh. coli	31	0	31
Klebsiella spp	13	10	3
Proteus mirabilis	15	5	10
Proteus vulgaris	2	2	0
Ps auriginosa	12	4	8
Enterococcus	13	3	10
Staph.saprophyticus	5	0	5
Staph.aureus	8	0	8
Staph.epidermidis	18	6	12
β-strep. group B	8	0	8

As is clear from the table in the majority of cases no growth of the respective bacterial strains was obtained.

EXAMPLE 2

Catheters were made from the same plastic material as in Example 1 but this time while adding the chlorhexidine in the starting material by admixing therein before transfer to the feeder funnel. The following quantities chlorhexidine were added:

Test catheter	A1	0.5 g	chlorhexidine	per	kg	of plastic
" "	A2	1.0 g	"	"	"	"
" "	A3	2.0 g	"	"	"	"
" "	A4	5.0 g	"	"	"	"
" "	A5	10.0 g	"	"	"	"

All catheters were tested against 22 different strains of E.coli, the growth being made submersive to ensure that the test strain grew and not a contaminant. The results of these tests are presented in Table 2.

TABLE 2

Strain	Catheter A1	A2	A3	A4	A5
E. coli 6	+	+	o	o	o
7	+	+	+	+	o
8	+	+	o	o	o
9	+	o	o	o	o
10	+	+	+	o	o
11	+	+	+	+	o
12	+	+	+	o	o
13	+	o	o	o	o
14	+	o	o	o	o
15	+	+	+	o	o
16	+	+	o	o	o
17	+	+	+	+	o
18	+	o	o	o	o
19	+	+	+	o	o
20	+	+	+	+	o
21	+	+	o	o	o
22	+	o	o	o	o
23	+	o	+	+	o
24	+	+	+	o	o
25	+	+	+	o	o
26	+	+	+	o	o
27	+	+	+	o	o

Note + = growth of test strain o = no growth

The table speaks its clear language and shows that a quantity of chlorhexidine of about 0.05% does not give any effect on growth, whereas at increasing concentration the chlorhexidine inhibition of the growth increases. Even if in many cases a concentration of 0.2% of chlorhexidine gives an effect it is clear from the table that it is preferred to use a quantity of hexidine of at least about 0.5% by weight, whereas for economical reasons it does not seem to be necessary to increase the concentration over about 1% by weight.

EXAMPLE 3

Catheters were manufactured in accordance with the technique according to Example 2 but instead of polyvinylchloride there was used a highmolecular polyethylene of low density of the type Lupolen® 1810D from BASF, DDR. Experiments were carried out with 12 different E.coli-strains while adding chlorhexidine to the plastic starting material in a quantity of 2 and 5 gs per kg, respectively. The results of the experiments are shown in Table 3.

TABLE 3

Bacterial strain	Polyethylenecatheter 2 gs/kg	5 gs/kg
E.coli 1	+	-
2	+	-
3	+	-
4	+	-
5	+	(+)
6	+	-
7	+	-
8	+	-
9	(+)	-
10	+	-
11	+	-
12	-	-

Note. +=growth and -= no growth

Further experiments have been made which verify the fact that autoclaving or washing of the plastic catheters containing chlorhexidine does not have any significant effect with regard to the bactericidal activity. Thus, the chlorhexidine is strongly anchored in the plastic, whereby the bactericidal effect can be maintained for a long period of time. In using the plastic objects according to the present invention thus for example catheters made in accordance with the invention can be left in position for longer periods of time without non-desirable infections arising.

CLAIMS

1. A plastic object intended for extended contact with living tissue, for example catheters , mainly consisting of a hydrophobic plastic, characterized thereby that it at least in connection with the surface contains chlorhexidine in a bactericidally effective amount.

2. A plastic object according to claim 1, characterized thereby that the chlorhexidine is baked into the plastic at least in the surface layer of the plastic object.

3. A plastic object according to claim 1 or 2, characterized thereby that the chlorhexidine is distributed in the whole plastic object.

4. A plastic object according to any preceding claim, characterized thereby that the hydrophobic plastic is polyvinylchloride.

5. A plastic object according to any of the claims 1-3, characterized thereby that the hydrophobic plastic is a polyolefin , for example polyethylene or polypropylene.

6. A plastic object according to any preceding claim, characterized thereby that the chlorhexidine is present in an amount of at least about 0.1% by weight based upon the part of the plastic containing same.

7. A plastic object according to claims 3 and 6, characterized thereby that the chlorhexidine is present in an amount within the range about 0.5 - about 1% by weight.

8. A process for the manufacture of a plastic object according to claim 1, containing extrusion of a thermoplastic in a manner known per se, characterized thereby that the thermoplastic in connection with the extrusion and before the cooling or self-cooling of the thermoplastic after leaving the nozzle is supplied with chlorhexidine in solid form in the desired quantity.

9. A process according to claim 8, characterized thereby that the chlorhexidine is added to the thermoplastic before feeding into the extruder thereby being distributed mainly evenly in the plastic object.

10. A process according to claim 8, characterized thereby that the chlorhexidine is added to the thermoplastic in connection with the nozzle, whereby it is found mainly only in the surface layer of the plastic object.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE8500430

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 L 29/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 4	A 61 L 15/03, 29/00; A 61 K 31/03; A 01 N 25/08, /10
US Cl	604:265; 128:349; 424:16

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	EP, A1, 0 022 289 (THE PROTECTOR & GAMBLE COMPANY) 14 January 1981 & JP, 56045954 US, 4343788 CA, 1156932 US, 4479795	1-7
Y	DE, A, 1 111 780 (AMERICAN CYANAMID 27 July 1961	1-7
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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
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